REMARKS

The Official Action dated January 19, 2011 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 6 is amended to more clearly recite the remedy for ophthalmic disease and claim 21 is amended to more clearly recite the disease conditions. Claim 12 is amended to correct a typographical error. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 2-6, 8-15 and 21-23 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner questioned if the term "ocular infection" refers to the other disease states recited in claim 21. The Examiner also questioned in claim 6 if ketotifen fumarate and diclofenac sodium are remedies for all of the disease states of claim 21.

This rejection is traversed. Claim 21 clearly recites the disease condition is selected from ocular infection of conjunctiva, lacrimal tissue or cornea, and a group of additional, distinct diseases. Claim 6 clearly recites that ketotifen fumarate is an antiallergic agent and diclofenac sodium is a nonsteroidal anti-inflammatory agent. Accordingly, these claims, and remaining claims 2-5, 8-15, 22 and 23 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, and the rejection has been overcome. Reconsideration is respectfully requested.

Claims 2-5, 8-15 and 21-23 were rejected under 35 U.S.C. §103(a) as unpatentable over Tojo et al, WO 01/26648, using its English equivalent US 7,052,714, in view of Patel et al, "Ocular Manifestations of Autoimmune Disease". Claims 5, 6 and 21 were also rejected under

35 U.S.C. §103(a) as unpatentable over Tojo et al in view of Patel et al and Takeuchi et al, US 5,929,115. The Examiner asserted that the claims do not recite a method of treating a condition but rather recite a method of transferring a remedy and that such transfer is inherent in the method of Tojo et al when the composition with the recited components is applied to the skin of an eyelid. The Examiner noted that Tojo et al teach the use of corticosteroids (prednisolone) for conditions such as intrinsic uveitis caused by autoimmune mechanism or abnormal immune response, and that the Becker et al publication cited in the Official Action of June 22, 2010 evidences that such corticosteroids are anti-inflammatories/antiallergics. The Examiner relied on Patel et al as teaching that intrinsic uveitis caused by autoimmune mechanism includes uveitis caused by autoimmune conditions such as systemic lupus erythematosus and psoriatic arthritis, and that these autoimmune conditions present with other ocular manifestations such as conjunctivitis, keratitis, and scleritis. From this, the Examiner concludes the patient population of claim 21 is encompassed or overlapped by the patient population of Tojo et al and therefore that the application of the patch taught by Tojo et al would intrinsically treat patients who may have the conditions of claim 21. The Examiner also referred to Table 8 of Tojo et al to assert that percutaneous transfer occurred not only in the posterior portion of the eye but was also present in other ocular tissues including the cornea and the sclera. Finally, the Examiner relied on Takeuchi as teaching the diclofenac sodium of claim 6.

However, Applicants submit that the method of claim 21, and the methods of claims 2-5, 8-15, 22 and 23 dependent thereon, are nonobvious over and are patentably distinguishable from Tojo et al in view of Patel et al and Takeuchi. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 21, the present invention is directed to a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group consisting of ocular infection of conjunctiva, lacrimal tissue or cornea; allergic conjunctivitis; pollinosis; vernal conjunctivitis; conjunctivitis; blepharitis; keratitis; corneal tumor; dacryocystitis; superficial keratitis; marginal blepharitis; scleritis; hordeolum; tarsadenitis; and trachoma. Thus, the transfer is to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group, and the remedy is for treatment of the disease. The method comprises applying a pressure-sensitive adhesive tape preparation comprising a plaster layer provided on a support, to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy for ophthalmic disease in the plaster layer to the external ophthalmic tissue by percutaneous permeation. The plaster layer contains the remedy for ophthalmic disease and a pressure-sensitive adhesive. Importantly, the remedy for ophthalmic disease is transferred by percutaneous permeation to the external ophthalmic tissue from the skin surface, and the amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow. Thus, the percutaneous permeation is substantially without systemic drug delivery.

Tojo et al is directed to an ophthalmic transdermal patch for treating diseases of the posterior segment of the eye, i.e., the lens, the vitreous body, the choroids and the retina (see, for example, column 1, lines 6-9). Tojo et al teach that their patch delivers drug to blood plasma and

the blood flow then delivers the drug to the posterior segment of the eye. Tojo et al disclose that the transferability of drugs to tissues including the iris-ciliary body, vitreous body and retina-choroid is high but no drug is found in the aqueous humor (column 13, lines31-32 and 50-52). Tojo et al disclose that the patch may be applied to the skin of an eyelid, the corner or other periphery of the eye, or a portion near the eye, such as the temple. However, Tojo et al do not suggest, disclose or recognize that a percutaneous absorption type transfer of a preparation for treatment for ophthalmic disease to an external ophthalmic tissue can advantageously occur when the preparation is applied to a skin surface including a front surface of an eyelid *substantially without* being transferred through a systemic blood flow, i.e., in a manner opposite to that desired by Tojo et al. Particularly, Tojo et al do not suggest, disclose or recognize that the amount of the remedy transferred to an external ophthalmic tissue by such an application within 8 hours after the application amounts to at least twice as much (mg/g•tissue) as the amount of the remedy transferred to the external ophthalmic tissue through the systemic blood flow.

The Examiner referred to Table 8 of Tojo et al to assert that percutaneous transfer occurred not only in the posterior portion of the eye but was also present in other ocular tissues including the cornea and the sclera. However, Table 8 of Tojo et al shows the results of experiments in which a patch was applied *on the abdominal region*, not on a front surface of an eyelid as required by claim 21. Moreover, since Tojo et al are concerned with systemic drug delivery, one of ordinary skill in the art would not expect the location of the Tojo et al patch to significantly effect the systemic drug delivery. Accordingly, one of ordinary skill in the art, reviewing the experimental results in Tojo et al's Table 8, has no apparent reason to consider that drug is transferred from the patch to abdominal skin, from the abdominal skin to the skin about the eyelid, and then from the skin about the eyelid to either an anterior or posterior portion of the

eye as asserted by the Examiner. Thus, Tojo et al do not show or demonstrate any intrinsic or inherent percutaneous transfer as presently claimed. In fact, Table 8 of Tojo et al discloses that the drug was not detected in aqueous humor (column 13, lines 31-32), preventing one of ordinary skill in the art from concluding that drug is transferred from the anterior ocular segment to the posterior ocular segment.

Thus, while Tojo et al teach transfer of a remedy for a disease of the posterior segment of the eye through systemic blood flow, Tojo et al do not render obvious a method using percutaneous absorption for transfer of a remedy for external ophthalmic tissue disease by application to the skin of the eyelid, *substantially without* being transferred through a systemic blood flow, i.e., in a manner opposite to that desired by Tojo et al.

the Examiner asserted at pages 13-14 of the Official Action that the improved drug delivery provided by the percutaneous permeation method of the present invention is not persuasive as drug transfer intrinsically occurs once the composition is placed in the area recited. However, Tojo et al do not demonstrate such a placement by example and provide no suggestion or recognition that transfer of a remedy for a ophthalmic disease to an external ophthalmic tissue will result predominately by percutaneous permeation, rather than by Tojo et al's desired systemic blood flow, in such a method. However, importantly, inherency (or "intrinsic" as the Examiner has asserted) is not synonymous with obviousness, and the fact that a result would be inherent in an obviousness rejection under 35 U.S.C. §103 cannot substitute for a showing of reasonable expectation of success, *In re Rinehart*, 531 F.2d 1048 (CCPA 1976).

The Examiner has relied on Patel et al and the previously cited Becker et al to conclude the patient population of claim 21 is encompassed or overlapped by the patient population of Tojo et al and therefore that the application of the patch taught by Tojo et al would intrinsically

treat patients who may have the conditions of claim 21. However, as noted, the fact that a result would be inherent in an obviousness rejection under 35 U.S.C. §103 cannot substitute for a showing of reasonable expectation of success, *In re Rinehart*, supra. Additionally, that a patient of Tojo et al may have had a disease as recited in claim 21 does not mean that a patient necessarily had such a disease. To establish obviousness under 35 U.S.C. §103, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic, *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Rather, to establish inherency, it must be clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill; inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient, *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). The Examiner has not clearly established that Tojo et al's patients have a disease as recited in claim 21 or that the claimed remedy transfer has inherently occurred.

Specifically, while Tojo et al broadly refer to application to the eyelids, an example thereof is not provided and there is no recognition that application to an eyelid transfers a drug to external ophthalmic tissue having a disease as claimed in an amount of at least twice as much as is delivered systemically over an eight-hour period as recited in claim 21. In view of the failure of Tojo et al to exemplify application of a transdermal patch to an eyelid, particularly to transfer a remedy for ophthalmic disease to an external ophthalmic tissue comprising conjunctiva, lacrimal tissue and/or cornea, and in view of the unexpected and unpredictable increased drug transfer by percutaneous permeation as compared with systemic administration in the present

method, the advantages of the method of claim 21 are unpredictable in view of the teachings of Tojo et al.

Finally, Takeuchi et al provide an anti-inflammatory eye drop comprising diclofenac sodium (DFNa) as an effective component, to which γ-cyclodextrin (γ-CyD), a water-soluble cyclodextrin, and polyvinylpyrrolidone (PVP) are added, exhibiting long-term storage stability and alleviating ocular irritation thereof. Takeuchi et al indicate that the anti-inflammatory eye drop does not cause any ocular irritation immediately after application in the eye, has long-term storage stability, and can be used in a wide range of the DFNa concentration. Takeuchi et al also describe that a high concentration of DFNa more conspicuously shows an intra-ocular prostaglandin-inhibitory effect and an atropine-induced mydriatic effect and therefore, not only shows marked effect in the maintenance of mydriasis and anti-inflammation during ocular surgery (of, for instance, cataract, glaucoma, retinal detachment, removal of vitreous body and strabismus), or in the therapeutic treatment after operations, but also shows effect of treating general eye diseases, i.e., various symptoms in which prostaglandin is involved, for instance, Behcet's disease, endogenous uveitis and inflammatory disease of outer ocular area (such as conjunctivitis, keratitis, episcleritis, pinguecula and hordeolum).

However, Takeuchi et al do not provide any teachings regarding a percutaneous absorption type preparation or method of using such a preparation. In addition, Applicants find no teaching by Takeuchi et al showing the effect of the eye drop on endogenous uveitis or inflammatory disease of an outer ocular area.

As shown in Table 1 in the present specification, the transdermal drug delivery method for treatment of ophthalmic diseases according to the present invention (Example 1) was recognized to have high transferability of ketotifen fumarate to the conjunctiva over a long

period of time while, in contrast, it was demonstrated that an eye drop ophthalmic solution (Comparative Example 1) is rapidly washed out by tears, and only a small amount of the drug remains 1 hour after administration, whereby potency over a long period of time cannot be expected (page 38, lines 9-18). The present methods therefore have a significant advantage over the use of eye drops as taught by Takeuchi et al. In this regard, Applicants note that Tojo et al also teach drops as adequate for administering a remedy to an external ophthalmic tissue, and therefore, like Takeuchi et al, teach away from the presently claimed methods for percutaneous transfer of a remedy for ophthalmic disease to an external ophthalmic tissue.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). Additionally, there must be a showing of a reasonable expectation of success from such a combination, *In re Rinehart*, supra. The combination of Tojo et al, Patel et al and Takeuchi et al fails to provide any apparent reason, absent the present specification teachings, to provide a method of transferring a remedy for ophthalmic disease to an external ophthalmic tissue by percutaneous permeation as presently claimed. Not only do these references fail to provide any reasonable expectation of success, they teach away from the claimed method by teaching the use of drops as a suitable transfer method and they fail to recognize the significant improvement of remedy transfer to an external ophthalmic tissue as compared with the systemic system of Tojo et al. Thus, the combination of Tojo et al, Patel et al and Takeuchi et al fails to render the present methods obvious, and the rejections under 35 U.S.C. §103(a) are therefore overcome. Reconsideration is respectfully requested.

Claims 2-6, 8-15 and 21-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over Higo et al, US 5,866,157, in view of Trimming et al, US 2001/0006968, Tojo et al, and Lerner et al, WO 97/18855. In response to the arguments set forth in Applicants' previous Amendment, the Examiner asserted that from Higo, transdermal patches are known to provide safe continuous delivery, and the secondary references are properly relied on for the respective teachings.

However, Applicants submit that claims 2-6, 8-15 and 21-23 are not rendered obvious over, and are patentably distinguishable from, the combination of Higo et al, Trimming et al, Tojo et al and Lerner et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The claimed methods for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue are discussed in detail above. While Higo et al disclose matrix type patch formulations which allow the physiological active substance to be absorbed via skin continuously into the circulating blood (column 6, lines 29-31), Applicants find no teaching by Higo et al relating to transferring a remedy to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea by percutaneous permeation and *substantially without* transfer through systemic blood flow. Similarly, Applicants find no teaching or suggestion by Higo et al to apply a patch to a front skin surface of an upper eyelid and/or lower eyelid as presently claimed. Test example 1 at column 16 applies patches to thawed human abdominal skin while Test example 2 at column 17 applies patches to normal human skin in the back region. Moreover, as Higo et al is concerned with delivering an active to blood for different diseases than recited in claim 21, the improvements of the present invention in delivering the remedy to the external ophthalmic tissue having a disease from the group defined

in claim 21 in a greater amount than through systemic blood flow delivery according to the present invention is neither recognized nor predictable in view of Higo et al. Specifically, Higo et al provide no teaching, suggestion or recognition that the amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application according to the present method amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

The Examiner asserted that the claimed method of transfer is intrinsic to the application of transdermal devices. However, as Higo et al do not disclose application of a patch to a front skin surface of an upper eyelid and/or lower eyelid as presently claimed, the presently claimed methods are not inherent in the teachings of Higo et al. Moreover, as neither Higo et al nor the secondary references teach that the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application as claimed within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow, the advantages of the present transfer methods are surprising and unpredictable over the cited combination of references.

Trimming et al teach an ophthalmic composition, for example, eye drops, comprising ketotifen for treatment of allergic conjunctivitis is compatible with soft contact lens (paragraph [0003]). Thus, while Higo et al are directed to systemic administration compositions, Trimming et al are directed to eye drops. One of ordinary skill in the art would have had no reason to combine any of the systemic administration composition teachings of Higo et al with the eye drops of Trimming et al as these two references relate to different administration routes and mechanisms and neither reference teaches, suggests or recognizes that application of a pressure-

sensitive adhesive tape preparation to a front skin surface of an upper eyelid and/or a lower eyelid as presently claimed transfers a remedy for ophthalmic disease to an external ophthalmic tissue by percutaneous permeation and *substantially without* transfer through systemic blood flow.

Tojo et al, as discussed above, discloses devices for transferring a remedy to plasma for systemic delivery to the posterior segment of the eye. While Tojo et al disclose that their preparations may be used to deliver drugs to the eye through the skin and other parts of the body and that the ophthalmic transdermal patches may be applied at any location of the body surface as desired, on a site relatively close to the eye, e.g., on the temple or around the eye, in particular on the skin of the eyelids or next to the lateral angle of the eye, Tojo et al fail to disclose application to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group of claim 21. Additionally, the in-vivo examples of Tojo et al, like those of Higo et al, employ the patches on the abdominal skin (column 9, lines 11 and 45) and on "the skin of the animals" (column 12, lines 35-39).

Moreover, since Tojo et al are concerned with systemic drug delivery, one of ordinary skill in the art would not expect the location of the Tojo et al patch to significantly effect the systemic drug delivery. Thus, Tojo et al, like Higo et al, fail to recognize that application to an eyelid transfers a remedy to external ophthalmic tissue having a disease as recited in claim 21 in an amount of at least twice as much as is delivered systemically over an eight-hour period as recited in claim 21. To the contrary, Tojo et al indicate that eye drops are satisfactory for treating external ophthalmic conditions. In view of the failure of Tojo et al to exemplify application of a transdermal patch to an eyelid, particularly to transfer a remedy to an external

ophthalmic tissue having a disease as recited in claim 21, and in view of the unexpected and unpredictable increased drug transfer by percutaneous permeation as compared with eye drops and systemic administration, the method of claim 21 is not suggested by the teachings of Tojo et al in combination with Higo et al.

Finally, Lerner et al disclose an iontophoresis device for enhancing the delivery of a drug into a selected organ or tissue, for example the brain, which device includes special electrodes connected with a selected energy source which maintains an energy field before and during the delivery of the drug. Beginning at page 37, line 34, Lerner et al disclose an embodiment for intracerebral transocularis wherein iontophoresis is conducted through the eyeballs. As noted by the Examiner, Lerner et al disclose that skin of the eyelid has a resistance lower than that on the rest of the skin surface and a resistance of the cornea and of the sclera is negligible. It is apparent that Lerner et al are referring to resistance to the flow of current, as Lerner et al further indicate that in this method, a split active electrode must be placed over the eyes and is covered by cotton or other material wetted in the solution of the necessary active substance and touching the skin as the electrodes themselves must not touch the skin, another split electrode covered by cotton or other material and wetted in the water is fixed on the mastoid processors or on another place or a single passive electrode is fixed on the back of the head in the area of cervical vertebrae or on another place, and, depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA (page 38, lines 2-18).

Thus, Lerner et al are concerned with administration of a drug to the brain by bypassing the blood-brain barrier using iontophoresis. One of ordinary skill in the art would have had no apparent reason to combine any of the teachings of Lerner et al with either the systemic administration compositions of Higo et al or Tojo et al, or the eye drops of Trimming et al.

Lerner et al's teaching of the resistance of the eyelids to the flow of current is simply irrelevant to the systemic administration of Higo et al and Tojo et al and to Trimming et al's eye drops.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, supra. Neither Higo et al nor Tojo et al teach a method for transferring a remedy for ophthalmic disease to an external ophthalmic tissue having a disease as recited in claim 21. Additionally, as Trimming et al and Lerner et al are directed to different and distinct modes of administration of actives, and none of these references provide any teaching of a method for percutaneously transferring a remedy to an external ophthalmic tissue having a disease selected from the group recited in claim 21, these references cannot be properly combined to result in the method of claim 21. Accordingly, combination of these references does not provide any apparent reason to one of ordinary skill in the art to have combined their elements in a manner that renders the method of claim 21 obvious, and the rejection under 35 U.S.C. §103 is therefore overcome. Reconsideration is respectfully requested.

Finally, claims 2-5, 8-15 and 21-23 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 3-7, 11 and 48 of copending application Serial No. 10/569,772 in view of Tojo et al. This rejection is traversed and reconsideration is respectfully requested.

Claim 21 is directed to a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from a specified group. The claims of copending application Serial No. 10/569,772 are directed to methods of promoting lacrimal fluid secretion by administration of a specified muscarinic receptor agonist. Applicants submit that

the copending application methods of promoting lacrimal fluid secretion using a specified muscarinic receptor agonist are distinct and nonobvious over methods for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group of claim 21. The respective claims are therefore directed to distinct conditions and therapies, whereby the rejection should be withdrawn. Reconsideration is respectfully requested. Moreover, in the event that the provisional double patenting rejection is the only rejection remaining in the present application, the rejection should be withdrawn in the present application, thereby permitting the present application to issue as a patent, MPEP §804.

It is believed that the above represents a complete response to Official Action, and places the present application in condition for allowance. In the event there are any outstanding issues relating to this application, the Examiner is urged to telephone the undersigned to efficiently resolve the same. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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